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Amend A

500.39147X00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Y. OSHIDA, et al
Serial No.:	09/678,652
Filed:	October 4, 2000
For:	METHOD OF INSPECTING A DNA CHIP AND AN APPARATUS THEREOF
Group:	1634
Examiner:	B. Sisson

AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

August 27, 2002

Sir:

The following amendments and remarks are respectfully submitted in connection with the above-identified application in response to the Office Action dated February 27, 2002.

IN THE CLAIMS:

Please amend claims 1-11 and 18-29 as follows:

1. (amended) A method of inspecting by irradiating a DNA chip with a plurality of M multi-spot excitation lights having a desired wavelength and of analyzing obtained fluorescent lights generated from said DNA chip, said DNA chip being obtained by hybridizing a target with DNA, said target being obtained by adding a desired fluorescent material to a DNA fragment formed by preprocessing from DNA that is an object to be inspected, said DNA chip including a plurality of L cells that are microscopic areas where a plurality of types of desired fragments are arranged in accordance with a predetermined rule, where M is the number of multi-spot excitation lights and L is the number of cells, comprising the steps of:

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irradiating mutually different positions of said DNA chip with said plurality of M multi-spot excitation lights simultaneously with the use of an objective lens for a time Δt that is longer than a fluorescent light attenuation time so as to generate fluorescent lights from said DNA chip, said multi-spot excitation lights having a spot diameter d that is smaller than a dimension D of said each cell of said plurality of L cells,

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guiding said generated fluorescent lights from said DNA chip to a fluorescent light detecting optical path,

separating and detecting said fluorescent lights from respective multi-spot lights generated by said multi-spot excitation lights irradiated onto said DNA chip, and

executing an inspection of said DNA chip in accordance with positions and intensities of said detected fluorescent lights so as to enable a determination of a kind and density of the hybridized target DNA.

2. (amended) The inspecting method as claimed in Claim 1, wherein said plurality of M multi-spot excitation lights are arranged in a 1-dimensional or 2-dimensional configuration with a fixed pitch on a straight line.

3. (amended) The inspecting method as claimed in Claim 1, further comprising the steps of:

arranging said plurality of M multi-spot excitation lights irradiated onto said DNA chip on a straight line with a spacing of kd with reference to said spot diameter d and an integer k, and

repeating an operation in sequence k times, said operation being an operation where, after said irradiation with said spot array has been performed during said time Δt, said array is displaced in a direction of said straight line by substantially d and

said irradiation is performed again during said time Δt, and thereby

executing said inspection toward kM spot positions in said straight line direction, and

displacing said DNA chip and said objective lens relatively at least in a direction perpendicular to said straight line direction, and thereby

inspecting a desired 2-dimensional area on said DNA chip.

a' cont

4. (amended) The inspecting method as claimed in Claim 1, further comprising the step of providing fluorescent light detection deflecting means within said fluorescent light detecting optical path so that said fluorescent lights generated by said plurality of M multi-spot excitation lights are synchronized with said displacement of said spot array in said array direction and come onto substantially the same location on said light-receiving apertures.

5. (amended) The inspecting method as claimed in Claim 4, wherein said fluorescent light detection deflecting means includes a wavelength selection beam splitter for permitting said excitation lights to pass therethrough and causing said fluorescent lights to be reflected.

6. (amended) The inspecting method as claimed in Claim 1, further comprising the step of providing a filter within said fluorescent light detecting optical path isolated from an excitation optical path, said filter permitting only said fluorescent lights to pass there-through and light-shielding said excitation lights.

7. (amended) The inspecting method as claimed in Claim 1, further comprising the step of forming said M multi-spot excitation lights by using a plurality of laser light-sources.

8. (amended) The inspecting method as claimed in Claim 7, wherein said M multi-spot excitation lights are obtained by the steps:

guiding, into optical fibers, said lights emitted from said plurality of laser light-sources, and

causing said lights to be emitted from light-emitting ends of said optical fibers, said light-emitting ends being aligned with M desired pitches.

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9. (amended) The inspecting method as claimed in Claim 1, wherein said excitation lights include a plurality of different wavelengths, and further comprising the step of distinguishing different targets on said DNA chip, a plurality of fluorescent materials having been added to said different targets.

10. (amended) The inspecting method as claimed in Claim 9, further comprising the steps of:

performing simultaneous irradiation with said excitation lights including said plurality of wavelengths, and thereby

distinguishing said different targets on said DNA chip so as to simultaneously detect said different targets in accordance with said plurality of fluorescent materials having been added to said different targets.

11. (amended) The inspecting method as claimed in Claim 1, further comprising the steps of:

irradiating a second light with an oblique incident angle on an inspection plane of said DNA chip;

detecting a reflection position at which said second light is reflected on said inspection plane; and

a1 cont. controlling a relative distance between said inspection plane and said objective lens in accordance with a result of detection of said reflection position.

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18. (amended) An inspecting method, comprising the steps of:

branching a laser beam so as to form eight or more beams, said laser beam being emitted from at least one laser light-source,

a2 irradiating an inspection plane of a DNA chip with said eight or more beams,

causing fluorescent lights to be generated from said DNA chip and separating said fluorescent lights from reflected lights of said beams so as to detect said fluorescent lights, and

inspecting said DNA chip in accordance with information on said fluorescent lights detected.

19. (amended) An inspecting method, comprising the steps of:

branching a laser beam into a plurality of beams having substantially the same intensity, said laser beam being emitted from at least one laser light-source,

projecting images of said plurality of branched beams onto an inspection plane of a DNA chip,

detecting images of fluorescent lights generated from said DNA chip by said projected images of said plurality of beams, and

inspecting said DNA chip in accordance with information on said detected images of said fluorescent lights.

20. (amended) The inspecting method as claimed in Claim 19, wherein said DNA chip is inspected by irradiating said DNA chip with said beams while displacing said DNA chip and said beams relatively in a 2-dimensional manner.

21. (amended) The inspecting method as claimed in Claim 19, wherein said DNA chip is irradiated with said branched beams located in a 2-dimensional manner.

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22. (amended) An inspecting method of irradiating a sample with multi-spot excitation lights so as to detect fluorescent lights generated from said sample, said sample attaching DNA with at least one fluorescent molecule, comprising the steps of:

separating said fluorescent lights from said multi-spot excitation lights, said fluorescent lights being emitted from respective multi spots obtained by irradiating said sample with said multi-spot excitation lights including M microscopic spots, where M is the number of microscopic spots,

detecting fluorescent light images of said fluorescent lights emitted from said sample with the use of a plurality of light detecting devices capable of executing a photon counting,

photon-counting, individually, each of photon signals obtained from said respective light detecting devices,

storing, individually, data of photon-counted numbers Npm detected by said respective light detecting devices,

changing positions of said multi-spot lights and a position of said sample relatively so as to store in sequence data of said photon-counted numbers from said respective light detecting devices,

collecting stored data on said photon-counted numbers over a desired range on said sample, and

constructing a fluorescent light image from said collected data so as to execute said inspection.

23. (amended) An inspecting method of irradiating a sample with sheet-shaped excitation lights so as to detect fluorescent lights generated from said sample, said sample attaching DNA with at least one fluorescent molecule, comprising the steps of:

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separating said fluorescent lights from said sheet-shaped excitation lights, said fluorescent lights being emitted from irradiation areas, said irradiation areas being obtained by irradiating said sample with said sheet-shaped excitation lights,

detecting fluorescent light images of said fluorescent lights emitted from said sample with the use of a plurality of light detecting devices capable of executing a photon counting,

photon-counting, individually, each of photon signals obtained from said respective light detecting devices,

storing, individually, data of photon-counted numbers Npm detected by said respective light detecting devices,

changing positions of said irradiation areas and a position of said sample relatively so as to store in sequence data of said photon-counted numbers from said respective light detecting devices,

collecting stored data on said photon-counted numbers over a desired range on said sample, and

constructing a fluorescent light image from said collected data so as to execute said inspection.

24. (amended) The inspecting method as claimed in Claim 22, wherein said M is equal to 10 or more.

25. (amended) The inspecting method as claimed in Claim 24, wherein said M is equal to 50 or more.

26. (amended) The inspecting method as claimed in Claim 22, wherein said multi-spots are arranged on a 1-dimensional straight line or a 2-dimensional array.

C3 CA 27. (amended) The inspecting method as claimed in Claim 22 or 23, wherein said multi-spot excitation lights or said sheet-shaped excitation lights are colored lights having 2 or more wavelengths.

28. (amended) A method of inspecting a DNA chip by detecting fluorescent lights generated from a fluorescent material on a DNA sample, comprising the steps of:

separating said fluorescent lights from excitation lights irradiated onto said DNA sample, said fluorescent lights being emitted from respective multi-spots or sheet-shaped irradiation locations on said DNA sample that is obtained by irradiating said DNA sample with said excitation lights in the form of multi-spot excitation lights or sheet-shaped excitation lights, said multi-spot excitation lights including M microscopic spots, where M is the number of microscopic spots,

detecting fluorescent light images from said fluorescent lights emitted from said DNA sample with the use of a plurality of M light detecting devices in an average pixel detecting time of (300 μsec/M) or less,

storing, individually, signals obtained from said respective light detecting devices,

changing, relatively, positions of said multi-spot lights or said sheet-shaped excitation lights and a position of said DNA sample so as to store said signals in sequence,

collecting said stored signals over a desired range on said DNA sample, and

constructing a fluorescent light image from said collected and stored signals.

29. (amended) A method of inspecting a DNA chip by detecting fluorescent lights generated from a fluorescent material on a DNA sample, comprising the steps of:

separating said fluorescent lights from excitation lights irradiated onto said DNA sample, said fluorescent lights being emitted from respective multi-spots or sheet-shaped irradiation locations on said DNA sample that is obtained by irradiating said DNA sample with said excitation lights in the form of multi-spot excitation lights or sheet-shaped excitation lights, said multi-spot excitation lights including M microscopic spots having a diameter or focus-achieving width which is smaller than 3 μm and larger than 0.3 μm, said sheet-shaped excitation lights having a width that is smaller than 3 μm and larger than 0.3 μm, where M is the number of microscopic spots,

detecting fluorescent light images emitted from said DNA sample with use of a plurality of light detecting devices,

storing, individually, signals obtained from said respective light detecting devices,

changing, relatively, positions of said multi-spot lights or said sheet-shaped excitation lights and a position of said DNA sample so as to store said signals in sequence,

collecting said stored signals over a desired range on said sample, and

constructing a fluorescent light image from said collected signals.

REMARKS

Applicants note that claims 12-17 and 30-35 stand withdrawn from consideration.

By the present amendment, claims 1-11 and 18-29 have been amended to clarify features thereof in a manner which is considered to overcome the rejection of claims 1-11 and 18-29 under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §101, as will be discussed below.

At the outset, applicants note that all claims under consideration in this application have been amended to recite an inspecting method or method of inspecting a DNA chip or sample, with a plurality of excitation lights utilizing an apparatus as illustrated in Fig. 1 of the drawings of this application, for example. It is noted that in the heading "Background of the Invention", there is described an apparatus and method for inspecting of DNA chips or the like and difficulties encountered therewith. Thus, the Examiner's rejection of claims 1-11 and 18-29 under 35 U.S.C. §101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility is not understood, in that the specification of this application describes different apparatus and method for inspecting of a DNA sample or chip, which enables determination of a kind and density of the hybridized target DNA, as described.

By the present amendment, inspection of the DNA chip or sample is effected based upon information of detected fluorescent lights which are generated from generated from the sample in response to irradiation of the sample with the excitation lights. As such, applicants submit that the rejection of claims 1-11 and 18-29 under 35 U.S.C. §101 is traversed, and applicant submit that the features as now recited in claims 1-11 and 18-29, as amended, should be considered to be in compliance with 35 U.S.C. §101, in that a sample is inspected in the manner defined and has utility described in the application.

As to the rejection of claims 1-11 and 18-29 under 35 U.S.C. §112, second paragraph, as being indefinite and under 35 U.S.C. §112, first paragraph, in that the claimed invention is not supported by either a specific asserted utility or a well

established utility, such rejections are traversed insofar as they are applicable to the present claims.

With respect to the rejection under 35 U.S.C. §112, first paragraph, applicants submit that the specification of this application describes a utility for the inspection method claimed, and the apparatus and method for carrying out the inspection is clearly described and illustrated. Thus, the rejection under 35 U.S.C. §112, first paragraph, should now be overcome.

With respect to the rejection under 35 U.S.C. §112, second paragraph, applicants submit that the various points raised by the Examiner have been overcome by the amendments of claims 1-11 and 18-29. Looking to claim 1, for example, this claim has been amended to recite a method of inspecting by irradiating a DNA chip (which is represented by reference numeral 2 in Fig. 1), with a plurality of M multi-spot excitation lights having a desired wavelength (which is represented by the lights from the microlens array 14 in Fig. 1) and analyzing obtained fluorescent lights generated from the DNA chip, which DNA chip is obtained by hybridizing a target with DNA, the target being obtained by adding a desired fluorescent material to a DNA fragment formed by preprocessing from DNA that is an object to be inspected, the DNA chip including a plurality of L cells (as illustrated in Fig. 2, for example), that are microscopic areas where a plurality of types of desired fragments are arranged in accordance with a predetermined rule, where M is the number of multi-spot excitation lights and L is the number of cells. As illustrated in Figs. 1-4, for example, mutually different positions of a DNA chip are irradiated with the plurality of M multi-spot excitation light simultaneously, with the use of an objective lens 16 as illustrated in Fig. 1 for a time Δt that is longer than a fluorescent attenuation time, so as to generate fluorescent lights from the DNA chip. The multi-spot excitation lights have a spot diameter d that is smaller than a dimension D of each cell of the plurality of L cells, and the generated fluorescent light from the DNA chip is guided to a

fluorescent light detecting optical path 3 as illustrated in Fig. 1. The fluorescent lights are separated and detected in the fluorescent light detecting optical path from respective multi-spot lights generated by the multi-spot excitation lights irradiated onto the DNA chip, and an inspection of the DNA chip is executed in accordance with positions and intensities of the detected fluorescent lights so as to enable a determination of a kind and density of the hybridized target DNA as described in the specification of this application. Applicants submit that the features as recited in claim 1 and the dependent claims as well as the other independent and dependent claims of this application, as amended, should now be considered to be in compliance with 35 U.S.C. §112, second paragraph, since the various points raised by the Examiner have been taken into account when amending such claims. Thus, applicants submit that claims 1-11 and 18-29 should now be considered to be in compliance with 35 U.S.C. §112, second paragraph.

In view of the above amendments and remarks, applicants submit that the claims under consideration, i.e. claims 1-11 and 18-29, should now be considered to be in compliance with 35 U.S.C. §101 and 35 U.S.C. §112, first and second paragraphs.

Since no art has been cited in rejecting claims of this application, applicants submit that since claims 1-11 and 18-29 should now be considered to be in compliance with 35 U.S.C. §101 and 35 U.S.C. §112, first and second paragraphs, claims 1-11 and 18-29 should now be in condition for allowance, and issuance of an action of a favorable nature is courteously solicited.

To the extent necessary, applicant's petition for an extension of time under 37 CFR 1.136. Please charge any shortage in the fees due in connection with the filing

of this paper, including extension of time fees, to Deposit Account No. 01-2135 (500.39147X00) and please credit any excess fees to such deposit account.

Respectfully submitted,

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